

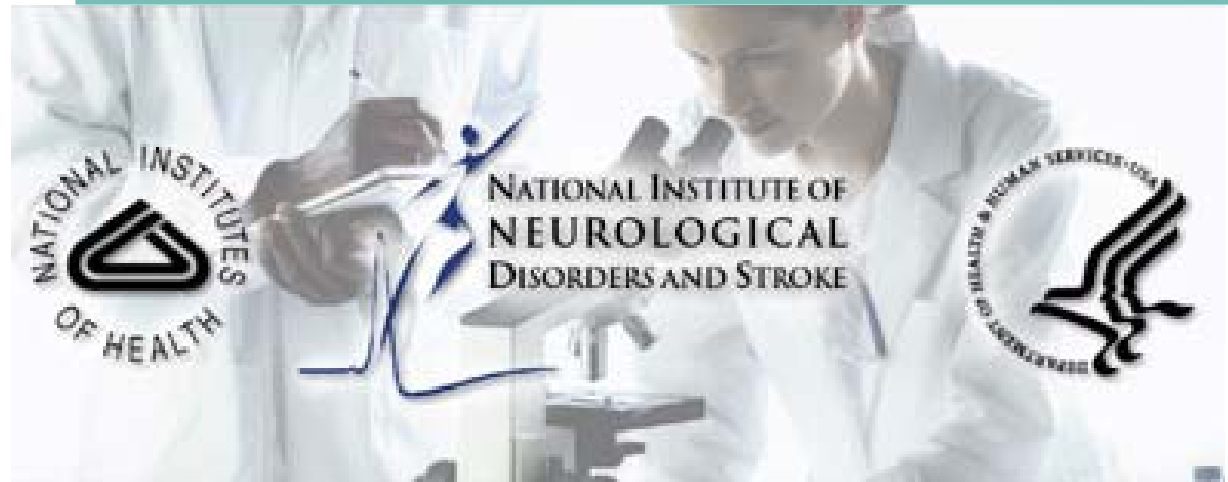
The SMA Project:

A New Approach to Therapy Development at NIH

Jill Heemskerk, Ph.D.

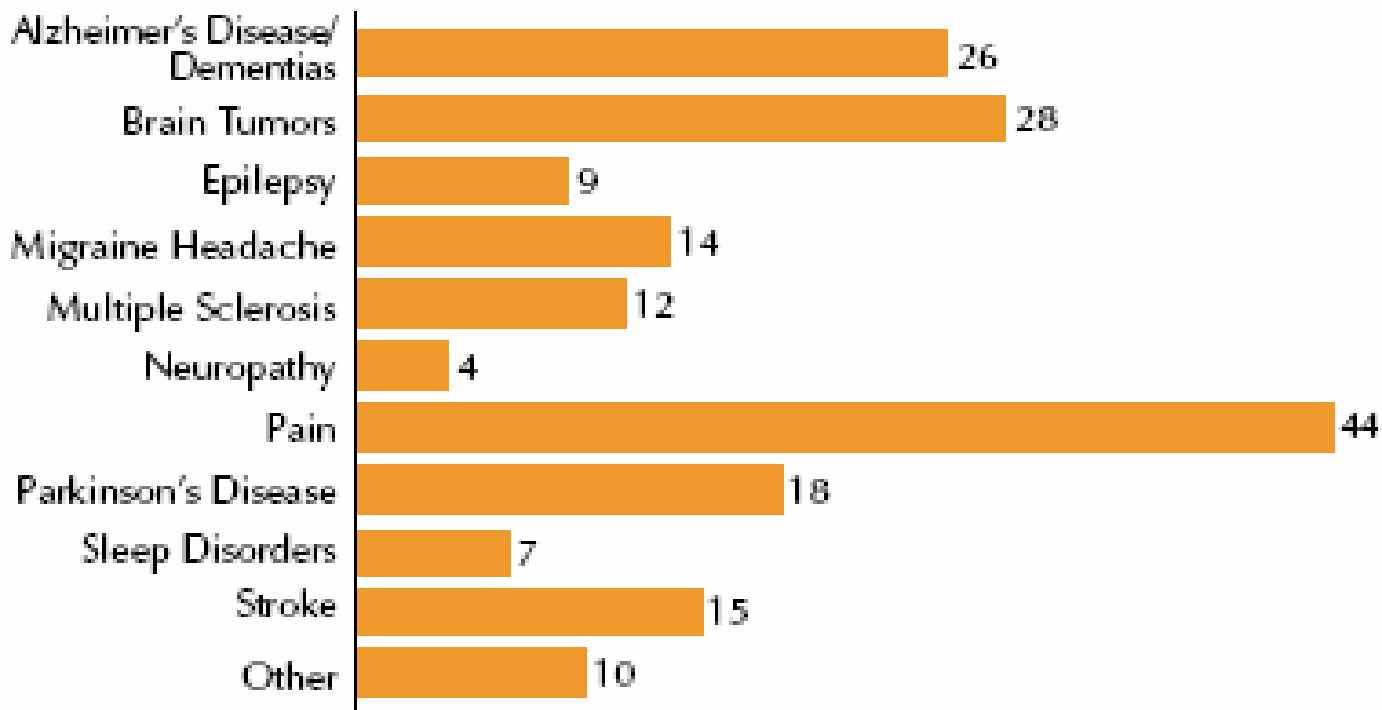
National Institute of Neurological Disorders and Stroke, NIH

July 13, 2006



Industry Neurotherapeutics: 19 Disorders

2003 MEDICINES IN DEVELOPMENT FOR NEUROLOGIC DISORDERS*



*Some medicines are listed in more than one category.

450 NINDS Disorders

[illegible]

The SMA Project

◆ What is it?

- An \$22MM NINDS therapeutics program for Spinal Muscular Atrophy (SMA)
- A pilot for other rare diseases

◆ Goal:

- New drugs for testing in SMA patients



Rationale for SMA as a Pilot

- ◆ Defined cause = loss of SMN1 gene
- ◆ Defined strategy for treatment = SMN2: identical protein, low expression
- ◆ Compounds that increase SMN2 expression



SMA Project Focus

Basic



Translational



Clinical

**SMA
Project**

Target ID
& Validation

Target
to Screen

Screen
to Hit

Hit to
Lead

Lead
Optimization

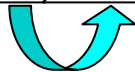
Candidate
Selection

Long-term
Toxicology

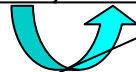
Clinical
Trials



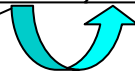
Target



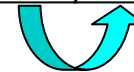
Assay



Hit



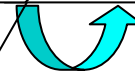
Lead



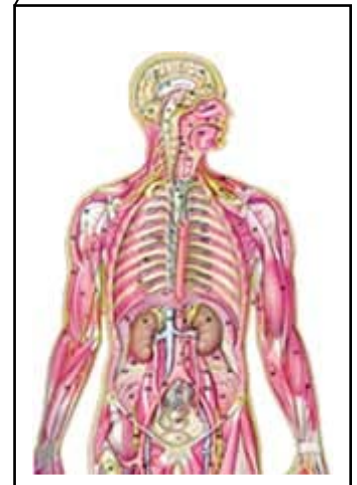
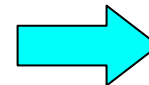
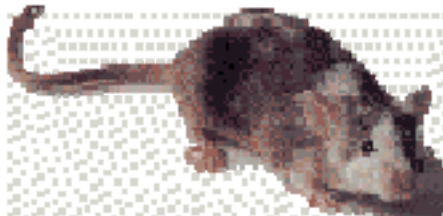
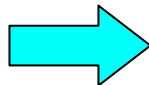
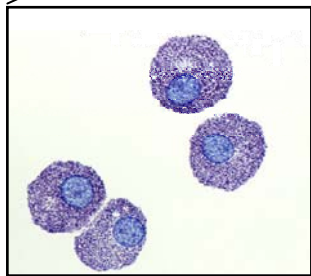
Pre-clinical
Candidate



Clinical
Candidate



IND



Scientific Steering Committee

- ◆ Chair: Robert Pacifici, CHDI, Inc. (formerly Lilly)
- ◆ John M. McCall, PharMac LLC (formerly Pfizer)
- ◆ Graham Johnson, Rib-X Pharmaceuticals (formerly BMS)
- ◆ Edward Hall, University of Kentucky (formerly Pharmacia & Upjohn)
- ◆ Perry Molinoff, Univ. of Pennsylvania (formerly BMS)
- ◆ Allan Tobin, High Q Foundation
- ◆ Howard Federoff, Rochester University
- ◆ Diana Escolar, Children's Hospital
- ◆ Richard Ransohoff, Cleveland Clinic
- ◆ Kurt Fischbeck, NINDS Intramural (ex officio)
- ◆ Tan Nguyen, FDA Orphan Products (ex officio)
- ◆ Jill Heemskerk, NINDS (ex officio)





NINDS/SAIC



CambridgeSoft®
Life Science Enterprise Solutions

Steering Committee

Lead Development
Team



Albany Molecular Research, Inc.®



Chemical
Optimization

In vitro
Testing

Pharm/Tox

Mouse
Model
Testing

CombinatoRx™

PSYCHOGENICS

Lead Development Team

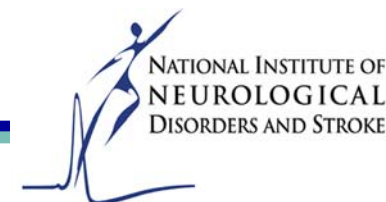
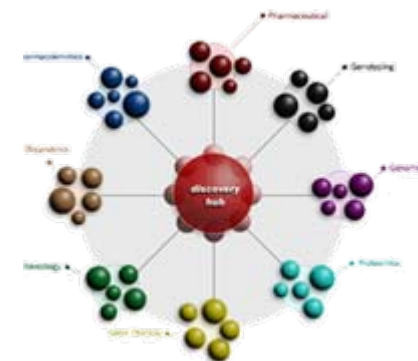
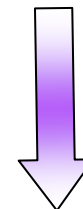
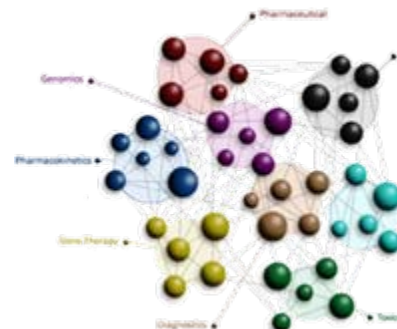
Chair: John McCall

◆ Chemistry

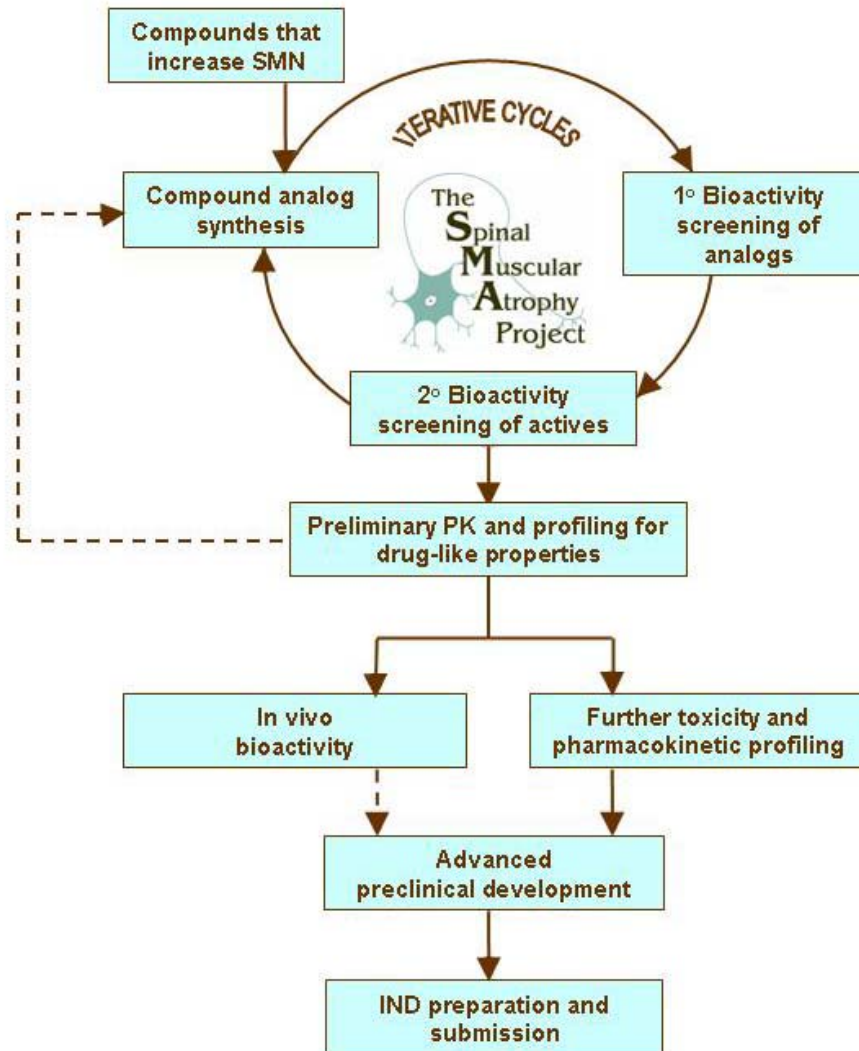
- John McCall, PharMac, LLC
- Graham Johnson, Rib-X
- Weifan Zheng, UNC

◆ Biology

- Keith Houck, EPA
- Jill Heemskerk, NINDS
- Sabina Robinson, SAIC

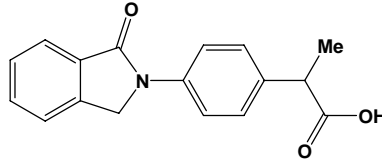


SMA Project Drug Discovery & Development Testing Funnel



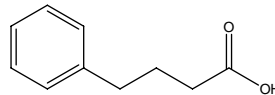
Starting Scaffolds

Indoprofen



- ◆ Increases SMN protein in vitro (Lunn et al, 2004)
- ◆ Improves *in utero* survival of SMA mice (Lunn et al 2004)

Phenylbutyrate:

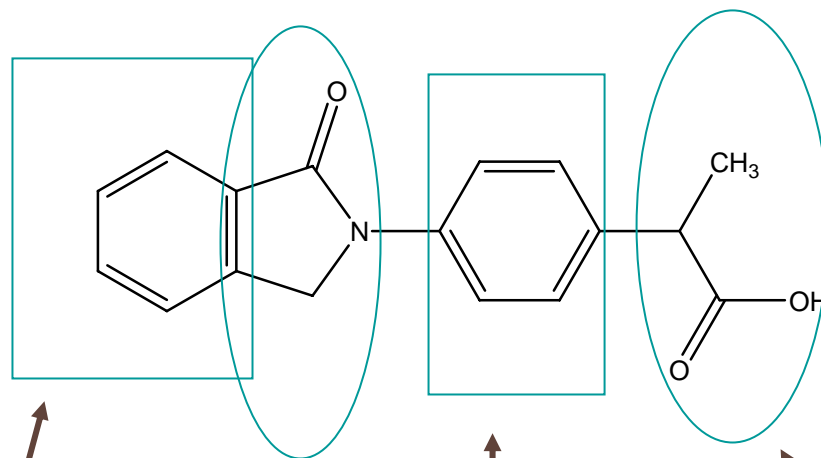


- ◆ Increases SMN expression in vitro (Andreassi et al 2004)
- ◆ Extends survival of SMA mice (Burghes, unpublished)

Indoprofen Structure Activity Strategy

SAR Goals

- ◆ Increase potency
- ◆ Eliminate toxicity
 - Cox Inhibition
- ◆ Improve BBB penetration



Benzo
Substitutions:
alkyl, halo,
methoxy,
cyano, amino,
aryl, heteroaryl

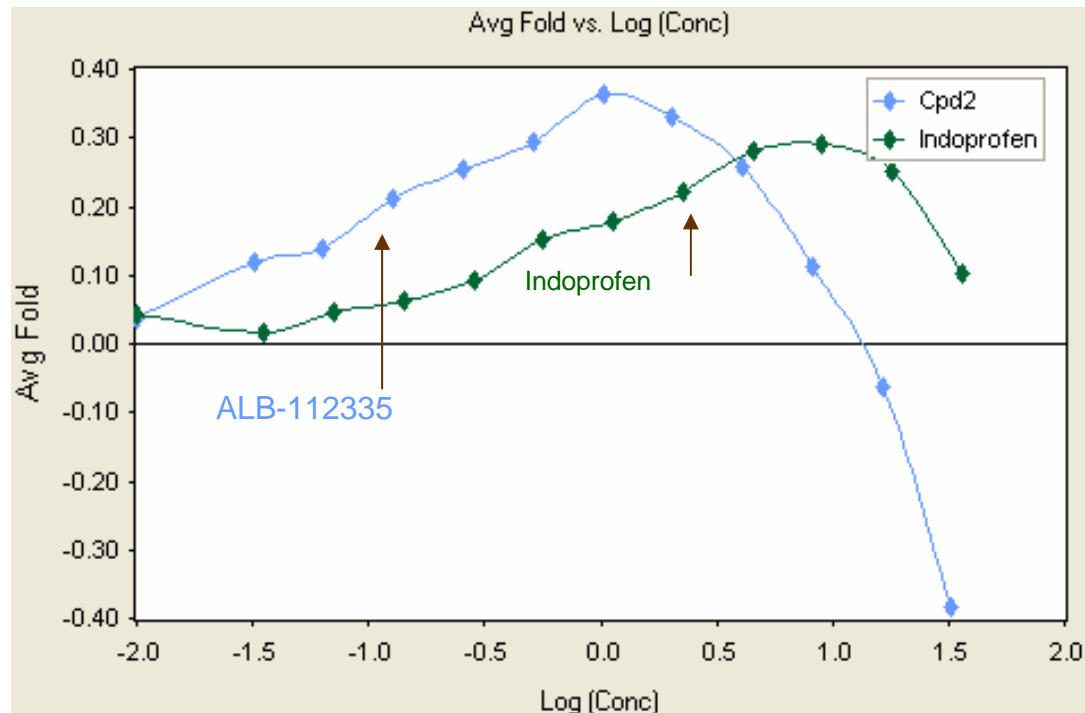
Lactam
Varied
heterocycle

Phenyl
Substitutions:
alkyl, halo,
methoxy, aryl,
heteroaryl

Acetic Chain
Varied at
methyl site,
length of
chain, and
CO₂H

Indoprofen SAR is Tractable

552 Analogs tested in Androphy splice reporter assay
145 Analogs with improved activity in reporter assay



Improved Brain Distribution

	Brain to Plasma Ratio
Indoprofen	0.03
Analog #1	0.4
Analog #2	15

Improvements to Indoprofen

- Increased potency 200 fold
- Increased efficacy 2.5 fold
- Enabled brain delivery
- Abolished Cox inhibitory structure

Systematic In Vivo Testing

- Pharmacologic studies
 - Formulation
 - Oral bioavailability
 - Brain distribution
 - Maximum tolerated dose
- SMA mouse model
 - Survival
 - Body weight
 - SMN expression studies

Getting to patients...

SMA Project studies

- ❑ Characterize drug-like properties
- ❑ Safety studies
- ❑ IND filing

Beyond the SMA Project

- ❑ Early phase clinical trials
- ❑ Industry licensing for full development

“Industry-style” *not* Industry

- The SMA Project is a Collaborative Enabler
 - Developing licensing opportunities
(e.g., indoprofen analogs)
 - IP-neutral enabling of outside efforts
-

Lessons Learned

- Steering committee expertise
 - Industry advisors
 - Fresh scientific perspective
- Industry-style operation
 - Flow plan with advancement criteria
 - Service organizations provide rapid turnaround
- Intensive project management
 - Tight, centralized coordination of projects
 - Internal expertise (Lead Development Team)

Applying the Pilot to Other Diseases

- Neurotherapeutics program coming in 2007
 - Medicinal Chemistry Service Facility
 - Central NIH Project Management
 - Flow Plan-driven projects
 - Resource leveraging
-

Acknowledgements

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- Meg Winberg
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- Charlotte Sumner